REMARKS

Claims 10 to 24 are under consideration in the present application. By this communication, claim 12 has been canceled and claims 10 and 21 have been amended. No new matter is added by the amendments submitted herewith as all claim language is fully supported by the specification and originally filed claims. The claims, as they will stand upon entry of the amendment, are attached herewith as Exhibit A.

Regarding the Specification

The disclosure is objected to because it contains embedded hyperlinks. In response to the objection, the specification has been amended to delete each occurrence of an embedded hyperlink and insert the respective uniform resource locator (url) in an information-only form, *i.e.*, not a hyperlink. Applicants respectfully submit that the amended specification is fully compliant with the guidelines in Manual of Patent Examining Procedure (MPEP) § 608.01.

The specification has also been amended to correct an inadvertent typographical error in the title of Table 5. As such, the amendment adds no new matter.

Rejection Under 35 U.S.C. § 112

The rejection of claims 10 to 13, 19 and 22 to 24 under 35 U.S.C. § 112 as allegedly lacking enablement is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that the claims are broadly drawn to a method for detecting any cellular proliferative disorder by detecting the methylation state of any nucleic acid. Amended claim 10 recites a method for detecting a cellular proliferative disorder associated with APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 in a subject. The method includes contacting a nucleic acid-

containing specimen from the subject with an agent that provides a determination of the methylation state of at least one gene or associated regulatory region of the gene. Only the methylation state of one or more specific genes including APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 and SDC4 is embraced by amended claim 10.

Applicants disagree with the Examiner's assertion that the specification does not provide "any correlation between tumor and normal tissue regarding hypermethylation of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 and SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders", (Office Action , page 5, paragraph 2). Applicants direct the Examiner's attention to Table 5 at page 39 of the specification which provides a listing of genes that are differentially methylated in disease tissue in comparison with normal tissue. For example, hypermethylation of ABOB (apolipoprotein B) is associated with common tumors; hypermethylation of CDX2 (caudal type homeo box transcription factor 2) is associated with leukemias, breast cancer and prostate cancer; hypermethylation of EGFR (epidermal growth factor receptor) is associated with leukemias and breast cancer; and hypermethylation of FBN1 (fibrillin-1) is associated with leukemias, colon cancer, breast cancer and prostate cancer. Table 5 further provides that hypermethylation of GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 and SDC4 are associated with various cellular proliferative disorders. In addition, the region of the each gene that is hypermethylated, *i.e.* the regions of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1and SDC4 containing CpG islands, is shown in Figure 4 and the nucleic acid sequences of each region are provided in SEQ ID NO:105 and SEQ ID NO:7 to SEQ ID NO:119. With the guidance provided in the specification, one of skill in the art would readily be able to practice invention methods for detecting a cell proliferative disorder associated with APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4.

Accordingly, Applicants respectfully submit that the specification fully enables claims 10 to 13, 19, and 22 to 24, and request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, second paragraph

The rejection of claims 10 to 24 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully traversed.

Claims 10 to 24 are allegedly indefinite because of the recitation of "cellular proliferative" in claim 10 (at line 8) and because "cellular proliferative" allegedly lacks antecedent basis. Applicants submit that those of skill in the art would understand exactly what is intended by the term "cellular proliferative". However, in order to facilitate prosecution of the present application, claim 10 has been amended as suggested by the Examiner to recite "cellular proliferative disorder".

Claim 21 is allegedly indefinite because it is not clear which consecutive primer pairs are intended by the claim language. In response, claim 21 has been amended to recite each primer pair embraced by claim 21.

Rejection Under 35 U.S.C. § 102(b)

The rejection of claims 10 to 11, 13, 19 and 22 to 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by Nelson *et al.* (U.S. Patent No. 5,552,277; hereinafter "Nelson") is respectfully traversed.

The present invention is directed to a method for detecting a cellular proliferative disorder associated with aberrant methylation of the gene APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4. The method to determine aberrant methylation includes contacting a nucleic acid-containing specimen from the

subject with an agent that provides a determination of the methylation state of at least one of the genes or an associated regulatory region of the genes. Only Applicants provide methylated forms of the genes APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4. Only Applicants identified the T-type calcium channel, CACNA1G, and its association with proliferative cell disorders such as colorectal cancers, colorectal adenomas, gastric cancers and acute myelogenous leukemia. In contrast, Nelson teaches a method of detecting a prostate cancer by determining the presence of hypermethylated glutathione-S-transferase (GSTP1). Nelson does not teach or suggest that any other cell proliferative disorders can be detected by invention methods, nor does Nelson teach that methylation of any genes other than GSTP1 are indicative of prostate cancer or any other cell proliferative disorder. Therefore, Nelson does not anticipate Applicants' invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 10 to 11, 13, 19 and 22 to 24 under 35 U.S.C. § 102(b).

The rejection of claims 10 to 11, 13, 19 and 22 to 24 under 35 U.S. C. § 102(b) as allegedly being anticipated by Baylin *et al.* (U.S. Patent No. 5,756,668, hereinafter "Baylin") is respectfully traversed.

Applicants invention relates to a method for detecting a cellular proliferative disorder associated with the gene APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 by detecting aberrant methylation of the genes. In contrast, Baylin teaches that one gene, a tumor suppressor gene named hypermethylation in cancer 1 (HIC-1), is aberrantly hypermethylated in multiple common tumor types. Baylin does not teach or suggest that hypermethylation of any specific gene other than HIC-1 is associated with tumors. Therefore, Baylin does not anticipate Applicants' invention. Accordingly,

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 10, 11, 13, 19 and 22 to 24 under 35 U.S.C. § 102(b).

Double Patenting Rejection

The rejection of claims 10, 11, 13 and 22 to 24 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1 and 3 of U.S. Patent No. 5,552,227 ("Nelson") is respectfully traversed.

Applicants respectfully disagree with the Examiner's assertion that the claims of the present application encompass the claims of Nelson. Amended claim 10 and claims dependent therefrom relate to a method for detecting a cellular proliferative disorder associated with the gene APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4. The method includes contacting a nucleic acid-containing specimen from the subject with an agent that provides a determination of the methylation state of at least one gene or associated regulatory region of the gene including APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 and SDC4. Claims 1 and 3 of Nelson relate to a method of detecting a prostatic cell proliferative disorder associated with glutathione-S-transferase. Nelson does not teach or suggest any cell proliferative disorder other than prostatic cell proliferative disorder. Furthermore, Nelson does not teach or suggest determining the methylation state of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4. Therefore, Applicants submit that the present claims are patentably distinct from claims 1 and 3 of Nelson. Accordingly, reconsideration and withdrawal of the double patenting rejection of claims 10, 11, 13 and 22 to 24 are respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is requested to telephone the undersigned at (858) 677-1456, so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: **April 26, 2001**

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Attachment: Exhibit A